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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/965,796	10/01/2001	David M. Goldenberg	018733-1060	3640

26633 7590 01/24/2006

HELLER EHRMAN WHITE & MCAULIFFE LLP
1717 RHODE ISLAND AVE, NW
WASHINGTON, DC 20036-3001

EXAMINER	
HARRIS, ALANA M	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 01/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/965,796	GOLDENBERG, DAVID M.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-27,36-45,47,52,55-89 and 91-97* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-27,36-45,47,52,55-89 and 91-97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/04/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 24-27, 36-45, 47, 52, 55-89 and 91-97 are pending.

Claims 28-35, 46, 48-51, 53, 54 and 90 have been cancelled.

Claims 24, 36-39, 52, 55 and 60-62 have been amended.

Claims 24-27, 36-45, 47, 52, 55-89 and 91-97 are examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

3. Applicant submitted an Information Disclosure Statement (IDS) on October 1, 2001 noting that the listed documents were submitted in parent application serial number 09/307,816 filed May 10, 1999. The Examiner has reviewed the parent application, as well as most of the documents therein. References A10, A12, A17 and A19 have been reviewed. The Examiner thanks Applicant for supplying the references.

Specification

4. The instant application properly reflects the current status of the parent application in the first line of the specification, see submitted Amendment to the specification on October 04, 2005.

5. The use of the trademarks, PROLEUKIN ®, TECELEUKIN ®, ALDRITHIOL ® and ACTIMMUNE ® have been properly noted in this application as indicated by the amendment to the specification, see Amendment submitted October 4, 2005.

Withdrawn Rejections

Claim Rejections - 35 USC § 112

6. The rejection of claims 24-27, 36-45, 47, 52, 55-89 and 91-97 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for human, humanized or chimeric anti-CD22 antibodies, does not reasonably provide enablement for fragments thereof is withdrawn in light of the amendments to the claims. Claims 28-35, 46, 48-51, 53, 54 and 90 were cancelled.

7. The rejection of claims 60-89 and 91-97 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn. Claim 90 was cancelled.

Claim Rejections - 35 USC § 102

8. The rejection of claims 24-26, 36-38, 44, 45 and 52 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent number 5,789,554 (filed July 31, 1996) is withdrawn in light of the claim amendments. Claims 28-35, 46, 48-51, 53 and 54 have been cancelled.

9. The rejection of claims 24-26, 36-38, 44, 45, 52 and 55-57 under 35 U.S.C. 102(b) as being anticipated by WO 96/04925 (22 February 1996/ IDS reference A8) is withdrawn in light of the claim amendments. Claims 28-35, 46, 48-51, 53 and 54 have been cancelled.

Claim Rejections - 35 USC § 103

10. The rejection of claims 24-26, 36-38, 44, 45, 47, 49, 52, 55, 56, 60-69, 73-77 and 91-93 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent number 5,789,554 (filed July 31, 1996), and in view of Li et al. (Cellular Immunology 118: 85-99, 1989) is withdrawn in light of the claim amendments. Claims 28-35, 46, 48-51, 53, 54 and 90 have been cancelled.

11. The rejection of claims 24-27, 36-38, 44, 45, 52, 55-57, 60-70, 73-77 and 91-93 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent number 5,789,554 (filed July 31, 1996), and further in view of U.S. Patent number 5,106,955 (April 21, 1992) is withdrawn. Claims 28-35, 46, 48-51, 53, 54 and 90 have been cancelled.

12. The rejection of claims 24-26, 36-42, 44, 45, 52, 55-57, 60-70, 73-77 and 91-93 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent number 5,789,554 (filed July 31, 1996), in view of U.S. Patent Number 5,686,072 (filed February 22, 1994/ IDS reference A1) and WO 95/09917 (April 13, 1995/ IDS reference A5) is withdrawn. Claims 28-35, 46, 48-51, 53, 54 and 90 have been cancelled.

13. The rejection of claims 24-26, 36-39, 44, 45, 52, 55-57, 60-70, 73-77 and 91-93 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent number 5,789,554 (filed July 31, 1996), in view of European Patent Application 0 510 949 A2 (October 28, 1992/ IDS reference A4) is withdrawn. Claims 28-35, 46, 48-51, 53, 54 and 90 have been cancelled.

14. The rejection of claims 24-27, 36-38, 43-45, 49, 51, 52, 55-89 and 90-97 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent number 5,789,554 (filed July 31, 1996), and further in view of U.S. Patent number 5,698,178 (filed April 8, 1998) is withdrawn. Claims 28-35, 46, 48-51, 53, 54 and 90 have been cancelled.

15. The rejection of claims 24-27, 36-38, 43-46, 52 and 55-97 under 35 U.S.C. 103(a) as being unpatentable over WO 96/04925 (22 February 1996/ IDS reference A8), and further in view of U.S. Patent number 5,698,178 (filed April 8, 1998) is withdrawn. Claims 28-35, 46, 48-51, 53, 54 and 90 have been cancelled.

Maintained and New Grounds of Rejection

Claim Rejections - 35 USC § 102

16. The rejection of claims 60-70, 73-79 and 91-93 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent number 5,789,554 (filed July 31, 1996) is maintained. Claim 90 has been cancelled.

Applicant argues that the reference does not "...describe an immunoconjugate where the therapeutic agent is attached indirectly via a linkage to the anti-CD22 or antibody fragments or is attached directly to the anti-CD22 antibody or antibody fragment-via a free sulhydryl group.", see Remarks submitted October 4, 2005, page 14, 4th paragraph. These arguments have been carefully considered, but found unpersuasive.

Applicant has amended claim 60 in order to obviate the instant rejection. However, U.S. Patent number 5,789,554 continues to disclose conjugates of chimeric and humanized chimeric LL2 antibodies with cytotoxic agents, labels, as well as therapeutic agents attached indirectly via linkages in therapy of B-cell lymphomas and leukemias, see last sentence of the Abstract; column 2, lines 56-62; column 20, lines 9-18. These antibodies of the taught method could be attached to cytotoxic agents, as well as chemotherapeutic drugs, chelators, fluorescent molecules, radionuclides or toxins, see column 5, lines 20-28; Example 9 of columns 19 and 20 and with particularity lines 9-18 in column 20. For the reasons of record and the facts presented in the preceding sentences the rejection is maintained.

17. The rejection of claims 60-70, 73-77, 79 and 91-93 under 35 U.S.C. 102(b) as being anticipated by WO 96/04925 (22 February 1996/ IDS reference A8) is maintained. Claim 90 has been cancelled.

Applicant argues that the reference does not "...describe an immunoconjugate where the therapeutic agent is attached indirectly via a linkage to the anti-CD22 or

antibody fragments or is attached directly to the anti-CD22 antibody or antibody fragment-via a free sulhydryl group.", see Remarks submitted October 4, 2005, page 14, 4th paragraph. These arguments have been carefully considered, but found unpersuasive.

Applicant has amended claim 60 in order to obviate the instant rejection. However, the WO document continues to disclose immunoconjugates comprising chimeric and humanized LL2 antibodies with cytotoxic agents, labels, as well as therapeutic agents attached indirectly via linkages in therapy of B-cell lymphomas and leukemias, see Abstract and page 1, lines 5-12; page 3, line 31-page 4, line 13; page 7, lines 27-38; and page 33, lines 15-24. The document reveals the implementation of fragments from both human and murine immunoglobulin chains in methods of treatment, see page 3, line 24-page 4, line 5; page 4, lines 14-32. A wide variety of diagnostic and therapeutic reagents can be conjugated to the disclosed antibodies such as doxorubicin, taxol, chelators, detectable labels such as fluorescent molecules, cytotoxic agents such as heavy metals or radionucleoides and toxins such as *Pseudomonas* exotoxin, see page 8, lines 17-26; page 33, lines 3-11; and page 33, line 33-page 34, line 10. The disclosed antibodies can be conjugated to a radioisotope other than ^{131}I for example ^{90}Y or ^{111}In using a chelating agent, see page 34, lines 3-10. For the reasons of record and the facts presented in the preceding sentences the rejection is maintained.

18. The rejection of claims 60-65, 67-69 and 91-95 are rejected under 35 U.S.C. 102(b) as being anticipated by Juweid et al. (Cancer Research (Suppl.) 55:5899s-5907s, December 1, 1995/ IDS reference A20) is maintained. Claim 90 has been cancelled.

Applicant avers the reference does not disclose or teach an immunoconjugate where the therapeutic agent is and/or the use of the claimed immunoconjugate in combination with a naked anti-CD20 mab"., see Remarks, page 14, 2nd paragraph.

Applicant has amended claim 60 in order to obviate the instant rejection. Applicant is reminded that the claims are drawn to a method and not an immunoconjugate product. Nonetheless, Juweid continues to read on the claims. Juweid discloses "[t]reatment of Non-Hodgkin's lymphoma with radiolabeled murine, chimeric [and] humanized LL2, an anti-CD22 monoclonal antibody, see title and entire article. These antibodies have a radioisotope attached directly via the chloramine-T or iodogen method, see page 5900s, column 1, "Preparation..." section. The monoclonal antibodies were radiolabeled with ^{131}I and prednisone was administered in one particular case and intrathecal chemotherapy and EPOCH chemotherapeutic regimen was administered in others, see page 5902s, column 1, middle of paragraph and column 2, "Initial Therapeutic..." section; and bridging sentence of pages 5902s and 5903s. The cumulative radioactive dose administered to patients ranged from 15.1 mCi ^{131}I-LL2 IgG to 343 mCi ^{131}I-LL2 F(ab')$_2$, which is within the range of 15 to 40 mCi stated by Applicant. For the reasons of record and the facts presented in the preceding sentences the rejection is maintained.

Claim Rejections - 35 USC § 103

19. Claims 24-26, 36-38, 44, 45, 47, 52, 55-57, 60-70, 73-79 and 91-93 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent number 5,789,554 (filed July 31, 1996), and in further view of Maloney et al. (Blood 84(8): 2457-2466, October 15, 1994/ IDS reference A11) and Li et al. (Cellular Immunology 118: 85-99, 1989). U.S. Patent number 5,789,554 teaches "[c]onjugates of chimeric and humanized chimeric LL2 antibodies with cytotoxic agents or labels... use[d] in therapy...of B-cell lymphomas and leukemias", see last sentence of the Abstract and column 2, lines 56-62. It is art known that LL2 antibodies are anti-CD22 monoclonal antibodies. The patent reveals the implementation of fragments from both human and murine immunoglobulin chains in methods of treatment, see column 2, lines 37-50; column 2, line 65-column 3, line 15.

These antibodies of the taught method could be attached to cytotoxic agents, as well as chemotherapeutic drugs, chelators, fluorescent molecules, radionuclides or toxins, see column 5, lines 20-28; Example 9 of columns 19 and 20 and with particularity lines 9-18 in column 20. The disclosed antibodies can be conjugated to a ^{131}I radioisotope, as well as ^{90}Y or ^{111}In using a chelating agent, see column 9, lines 35-40; column 20, lines 35-42.

The patent does not teach a method for a subject having a B-cell malignancy, *wherein the immunoconjugate comprises both,* at least one human, humanized or chimeric anti-CD22 antibody or a fragment thereof *and* a naked anti-CD20 monoclonal

antibody. U.S. Patent '554 also does not teach a therapeutic composition comprising at least two monoclonal antibodies that bind distinct CD22 epitopes.

However, Maloney teaches a method for treating B-cell lymphoma, Non-Hodgkin's lymphoma (NHL), as well as other leukemias and lymphomas with a chimeric anti-CD20 monoclonal antibody (also known as a naked anti-CD20 monoclonal antibody, IDEC-C2B8, C2B8, RITUXAN® (rituximab)) with a dosage ranging from 10-500mg/m2, see abstract. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer a therapeutic combination of antibodies of known anticancer antibodies to effectively treat B cell malignancies, Maloney, see page 2465, last paragraph. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in both references, that a mixture of antibodies to the different epitopes of would be more efficacious in therapeutic methods, as well as enhance the treatment modality, see Maloney, page 2465, last paragraph.

And, Li teaches that four anti-CD22 monoclonal antibodies, UV22-1, UV22-2, HD6 and RFB47 recognize CD22 A and B epitopes. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer a combination of antibodies to different CD22 epitopes, as taught in the Li reference in the method of treating B cell malignancies as taught in the patent. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in the Li reference, that a mixture of antibodies to

the different epitopes of CD-22 would be a more efficacious in therapeutic methods, as well as enhance the treatment modality.

20. Claims 24-27, 36-38, 44, 45, 52, 55-57, 60-70, 73-79 and 91-93 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent number 5,789,554 (filed July 31, 1996), and further in view of Maloney et al. (Blood 84(8): 2457-2466, October 15, 1994/ IDS reference A11) and U.S. Patent number 5,106,955 (April 21, 1992). Claims 28-35, 46, 48-51 and 90 have been cancelled. The teachings of patent #5,789,554 and Maloney have been presented in the previous cited 103(a) rejection. Those two references did not teach a method for treating a B-cell malignancy wherein the therapeutic composition comprises specifically chemotherapeutic drugs, a nitrosourea derivative, hormones and an antiviral toxin linked via crosslinking agents.

However, U.S. patent #5,106,995 teaches the specific chemotherapeutic drugs, nitrosourea and hormones and antiviral toxins, see entire page with columns 5 and 6. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer a therapeutic combination of a known anticancer antibody with other anticancer molecules in the method of treating B cell malignancies, as taught in both patents. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in the patents that conjugates of anti-CD22 antibodies and anti-CD20 mabs with anticancer agents are efficacious in the treatment of B-cell lymphomas and leukemias, see patent '554,

abstract and Example 9 of columns 19 and 20; Maloney, page 2465, column 1, last paragraph; and patent '955, abstract and columns 5 and 6.

21. Claims 24-26, 36-42, 44, 45, 52, 55-57, 60-70, 73-77 and 91-93 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent number 5,789,554 (filed July 31, 1996), in view of Maloney et al. (Blood 84(8): 2457-2466, October 15, 1994/ IDS reference A11), U.S. Patent Number 5,686,072 (filed February 22, 1994/ IDS reference A1) and WO 95/09917 (April 13, 1995/ IDS reference A5). Claims 28-35, 46, 48-51, 53, 54 and 90 have been cancelled.

The teachings of patent '554 and Maloney have been described in the initial 103(a) rejection. These references do not teach a multivalent fusion protein that additionally comprises at least one antibody component that binds with CD19 or a trivalent, tetravalent or quintavalent fusion.

However, U.S. patent #5,686,072 teaches the administration of an unconjugated anti-CD19 antibody (also regarded as a naked antibody), toxins (ricin, diptheria toxins in a mixture with anti-CD22 for the immunotherapeutic treatment of cancer, see abstract. It would have *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to combine an anti-CD19 antibody with an anti-CD22 antibody as taught in patent '072 . One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of both patents that the co-administration of anti-CD19 and anti-CD22 antibodies appears to provide a synergistic and advantageous cancer treatment, see both patents.

The WO document teaches that recombinant bispecific tetravalent antibodies are useful in both therapeutic and immunodiagnostic applications and can be produced with relative ease.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of claimed invention to produce a tetravalent construct comprising anti-CD22 antibodies, as well as trivalent and quintavalent fusion proteins. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in both patents and the WO document that tetravalent antibody constructs are more effective than monoclonal antibody to effectively target more antigenic sites on the cancer cells and to advantageously increase the avidity of antigen binding.

22. Claims 24-26, 36-39, 44, 45, 52, 55-57, 60-70, 73-77 and 91-93 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent number 5,789,554 (filed July 31, 1996), in view of in view of Maloney et al. (Blood 84(8): 2457-2466, October 15, 1994/ IDS reference A11) and European Patent Application 0 510 949 A2 (October 28, 1992/ IDS reference A4). Claims 28-35, 46, 48-51, 53, 54 and 90 have been cancelled.

The teachings of patent '554 and Maloney have been described in the initial 103(a) rejection. These references do not teach a therapeutic composition comprising the said anti-CD22 antibody and an immunomodulator, such as a CD19 antibody component and toxins.

However, EP 0 510 949 A2 teaches conjugate formulas comprising two moieties, wherein both have physiological activity, see column 3, lines 3-6. The moieties may be

an antibody and fragments thereof, interleukins 1-10, molecules that bind CD19 (regarded by the Examiner as an antibody), growth factors, GM-CSF, G-CSF and toxins (i.e., ricin, diptheria toxins) in a mixture with anti-CD22 for the immunotherapeutic treatment of cancer, see abstract and column 3, lines 24-47. It would have *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to combine efficacious anti-tumor agents within an anti-cancer therapeutic composition. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of both patents that such conjugate compositions provide a synergistic and advantageous cancer treatment, see both patents.

23. Claims 24-27, 36-38, 43-45, 52, 55-89 and 91-97 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent number 5,789,554 (filed July 31, 1996), and further in view of Maloney et al. (Blood 84(8): 2457-2466, October 15, 1994/ IDS reference A11) and U.S. Patent number 5,698,178 (filed April 8, 1998). Claims 28-35, 46, 48-51, 53, 54 and 90 have been cancelled.

The teachings of patent '554 and Maloney have been described in the initial 103(a) rejection. These references do not teach a method for treating a subjection having a B-cell malignancy comprising a therapeutic composition comprising a chemotherapeutic drug, immunomodulator, antiviral drugs, radioisotope, boron addend, anti-bacterial drug and photoactive agent or dye, as well as specific modes of attaching these molecules. Moreover, patent '554 and Maloney do not teach the administration

of the immunoconjugate comprising an anti-CD22 antibody with radioisotopes iodine and yttrium in the specific dosages set forth in claims 94-97.

However, U.S. patent #5,698,178 teaches specific radioisotopes, ^{198}Au, ^{32}P, ^{125}I, ^{90}Y, ^{186}Re, ^{188}Re, ^{67}Cu and ^{211}At; toxins, ricin A-chain, *Psuedomonas* endotoxin, gelonin, ribonuclease, abrin, and pokeweed antiviral protein; chemotherapeutic drugs, nitrogen msutards, alkyl sulfonates, nitrosoureas, triazenses, folic acid analogs, antiboitics, platinum coordination complexes, hormones, pyrimidine analogs; boron addends, such as carboranes; and immunomodulators, granulocyte-colony stimulating factor (G-CSF), GM-CSF, IL-1 and IL-3, see , see column 4, lines 35-56; column 6, lines 15-19; column 8, lines 26-36; column 16, line 59-column 17, line 2; column 23, line 11-column 24, line 6; column 31, lines 34-37. The patent also teaches the use of fluorescent chromogens or dyes, such as porphyrins in therapy termed photoradiation or photodynamic therapy in order to destroy a tumor population, see column 24, lines 7-31, 45-54. Patent '178 also teaches modes of attaching the therapeutic agents to the antibodies and antibody fragments, $F(ab')_2$, $F(ab)_2$, Fab' and Fab via chelators such as ethylenediaminetetraacetic acid , DPTA, polyethyleneglycol, TETA and a carrier polymer such as aminodextran, see column 15, lines 56-67; column 17, lines 57-67; column 20, lines 28-34; and column 23, lines 19-31. Attachment of therapeutic agents to anti-CD22 antibodies may be implemented via a free sulfhydryl group, see column 14, lines 28-38 and column 17, lines 57-67. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer

a therapeutic combination of a known anticancer antibody with other anticancer molecules in the method of B cell treatment.

Additionally, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer the naked anti-CD22 antibody in the recited dosages. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings well known in the art, that dosages of any pharmaceutical composition must be adjusted and optimized.

24. Claims 24-27, 38, 43-45, 52, 55-89 and 91-97 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/04925 (22 February 1996/ IDS reference A8), and further in view of Maloney et al. (Blood 84(8): 2457-2466, October 15, 1994/ IDS reference A11) and U.S. Patent number 5,698,178 (filed April 8, 1998). Claims 28-35, 46, 48-51, 53, 54 and 90 have been cancelled.

The WO document teaches immunoconjugates comprising chimeric and humanized LL2 antibodies with cytotoxic agents, labels, as well as therapeutic agents attached indirectly via linkages in therapy of B-cell lymphomas and leukemias, see Abstract and page 1, lines 5-12; page 3, line 31-page 4, line 13; page 7, lines 27-38; and page 33, lines 15-24. The document reveals the implementation of fragments from both human and murine immunoglobulin chains in methods of treatment, see page 3, line 24-page 4, line 5; page 4, lines 14-32. A wide variety of diagnostic and therapeutic reagents can be conjugated to the disclosed antibodies such as doxorubicin, taxol, chelators, detectable labels such as fluorescent molecules, cytotoxic agents such as

heavy metals or radionucleoides and toxins such as *Pseudomonas* exotoxin, see page 8, lines 17-26; page 33, lines 3-11; and page 33, line 33-page 34, line 10. The disclosed antibodies can be conjugated to a radioisotope other than ^{131}I for example ^{90}Y or ^{111}In using a chelating agent, see page 34, lines 3-10. The WO document does not teach a method for a subject having a B-cell malignancy, *wherein the immunoconjugate comprises both,* at least one human, humanized or chimeric anti-CD22 antibody or a fragment thereof *and* a naked anti-CD20 monoclonal antibody. Moreover, WO document 96/04925 does not teach the administration of the immunoconjugate comprising an anti-CD22 antibody with radioisotopes iodine and yttrium in the specific dosages set forth in claims 94-97.

However, Maloney teaches a method for treating B-cell lymphoma, Non-Hodgkin's lymphoma (NHL), as well as other leukemias and lymphomas with a chimeric anti-CD20 monoclonal antibody (also known as a naked anti-CD20 monoclonal antibody, IDEC-C2B8, C2B8, RITUXAN® (rituximab)) with a dosage ranging from 10-500mg/m2, see abstract. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer a therapeutic combination of antibodies of known anticancer antibodies to effectively treat B cell malignancies, Maloney, see page 2465, last paragraph. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in both references, that a mixture of antibodies to the different epitopes of would be more efficacious in therapeutic methods, as well as enhance the treatment modality, see Maloney, page 2465, last paragraph.

However, U.S. patent #5,698,178 teaches specific radioisotopes, ^{198}Au, ^{32}P, ^{125}I, ^{90}Y, ^{186}Re, ^{188}Re, ^{67}Cu and ^{211}At; toxins, ricin A-chain, *Psuedomonas* endotoxin, gelonin, ribonuclease, abrin, and pokeweed antiviral protein; chemotherapeutic drugs, nitrogen msutards, alkyl sulfonates, nitrosoureas, triazenses, folic acid analogs, antiboitics, platinum coordination complexes, hormones, pyrimidine analogs; boron addends, such as carboranes; and immunomodulators, granulocyte-colony stimulating factor (G-CSF), GM-CSF, IL-1 and IL-3, see , see column 4, lines 35-56; column 6, lines 15-19; column 8, lines 26-36; column 16, line 59-column 17, line 2; column 23, line 11-column 24, line 6; column 31, lines 34-37. The patent also teaches the use of fluorescent chromogens or dyes, such as porphyrins in therapy termed photoradiation or photodynamic therapy in order to destroy a tumor population, see column 24, lines 7-31, 45-54. Patent '178 also teaches modes of attaching the therapeutic agents to the antibodies and antibody fragments, $F(ab')_2$, $F(ab)_2$, Fab' and Fab via chelators such as ethylenediaminetetraacetic acid, DPTA, polyethyleneglycol, TETA and a carrier polymer such as aminodextran, see column 15, lines 56-67; column 17, lines 57-67; column 20, lines 28-34; and column 23, lines 19-31. Attachment of therapeutic agents to anti-CD22 antibodies may be implemented via a free sulfhydryl group, see column 14, lines 28-38 and column 17, lines 57-67. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the teachings of both documents to administer a therapeutic combination of a known anticancer antibody with other anticancer molecules in the method of B cell treatment.

Additionally, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer the naked anti-CD22 antibody in the recited dosages. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings well known in the art, that dosages of any pharmaceutical composition must be adjusted and optimized.

25. The rejection of claims 60-89 and 91-97 under 35 U.S.C. 103(a) as being unpatentable over Juweid et al. (Cancer Research (Suppl.) 55:5899s-5907s, December 1, 1995/ IDS reference A20) and U.S. Patent number 5,698,178 (filed April 8, 1998) is maintained. Claim 90 has been cancelled.

Applicant states that claim 60 has been amended to obviate the instant rejection and more particularly describe the claimed invention. Applicant also notes none of the cited references disclose all of the elements of the amended claims. These points of view has been carefully considered, but found unpersuasive.

The teachings of Juweid have been presented in the 102(b) rejection. Juweid does not teach wherein the therapeutic agent is ^{90}Y or ^{67}Cu attached via a free sulfhydrl group or by means of an aminodextran and the chelating agents are DPTA and TETA. Juweid also does not teach does not teach the administration of the immunoconjugate comprising an anti-CD22 antibody with radioisotopes iodine and yttrium in the specific dosages set forth in claims 94-97.

However, U.S. patent #5,698,178 teaches specific radioisotopes, ^{198}Au, ^{32}P, ^{125}I, ^{90}Y, ^{186}Re, ^{188}Re, ^{67}Cu and ^{211}At; toxins, ricin A-chain, *Psuedomonas* endotoxin, gelonin, ribonuclease, abrin, and pokeweed antiviral protein; chemotherapeutic drugs, nitrogen msutards, alkyl sulfonates, nitrosoureas, triazenses, folic acid analogs, antiboitics, platinum coordination complexes, hormones, pyrimidine analogs; boron addends, such as carboranes; and immunomodulators, granulocyte-colony stimulating factor (G-CSF), GM-CSF, IL-1 and IL-3, see , see column 4, lines 35-56; column 6, lines 15-19; column 8, lines 26-36; column 16, line 59-column 17, line 2; column 23, line 11-column 24, line 6; column 31, lines 34-37. The patent also teaches the use of fluorescent chromogens or dyes, such as porphyrins in therapy termed photoradiation or photodynamic therapy in order to destroy a tumor population, see column 24, lines 7-31, 45-54. Patent '178 also teaches modes of attaching the therapeutic agents to the antibodies and antibody fragments, $F(ab')_2$, $F(ab)_2$, Fab' and Fab via chelators such as ethylenediaminetetraacetic acid , DPTA, polyethyleneglycol , TETA and a carrier polymer such as aminodextran, see column 15, lines 56-67; column 17, lines 57-67; column 20, lines 28-34; and column 23, lines 19-31. Attachment of therapeutic agents to anti-CD22 antibodies may be implemented via a free sulfhydryl group, see column 14, lines 28-38 and column 17, lines 57-67. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the teachings of both documents to administer a therapeutic combination of a known anticancer antibody with other anticancer molecules in the method of B cell treatment.

Additionally, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer the naked anti-CD22 antibody in the recited dosages. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings well known in the art, that dosages of any pharmaceutical composition must be adjusted and optimized.

Double Patenting

26. The provisional rejection of claims 24-27, 36-45, 47, 52, 55-89 and 91-97 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 24-44 of copending Application No. 10/314,330 (filed December 9, 2002) is maintained. Claims 28-35, 46, 48-51, 53, 54 and 90 have been cancelled.

Applicant requests for the instant rejection to be held in abeyance until indication of allowable subject matter has been indicated at which time they will consider filing a terminal disclaimer.

The request has been considered, but found unpersuasive. At this point in prosecution the rejection is maintained for the reasons of record in listed in the first action on the merits (FAOM) mailed April 4, 2005.

Conclusion

27. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (571)272-0831. The examiner works a flexible schedule, however she can normally be reached between the hours of 7:30 am to 6:30 pm with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER

Alana M. Harris, Ph.D.
20 December 2005